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Carcinosarcoma of the Ovary

19 Years of Prospective Data from a Single Center

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BACKGROUND. A review of clinicopathologic features and outcome in women with carcinosarcoma of the ovary (also known as malignant mixed mesodermal tumor [MMMT]) compared with a group of women with serous adenocarcinoma (SAC) of the ovary was conducted.

METHODS. Between 1984 and 2002, 1568 patients with epithelial ovarian carcinoma and 70 patients with ovarian carcinosarcoma underwent treatment at the Edinburgh Cancer Centre. Analysis was performed on 65 patients with MMMT, and 746 patients with SAC were selected as a group for comparison. Baseline variables were recorded prospectively and response to chemotherapy and progression-free and cause-specific survival between the groups were compared.

RESULTS. Patients with carcinosarcoma had a mean age of 66.6 years, which is significantly older than those with SAC (62.0 years) ($P < 0.001$). The objective response rate to platinum-based chemotherapy was found to be significantly lower in patients with carcinosarcoma (25% vs. 60%; $P = 0.02$). Cause-specific survival in the carcinosarcoma group was poor and significantly shorter than that observed in the SAC group (median survival of 8.2 months vs. 20.7 months; $P < 0.0001$). Progression-free survival in patients with carcinosarcoma also was found to be significantly shorter compared with patients with SAC (median progression-free survival of 6.4 months vs. 12.1 months; $P < 0.001$). Achieving optimal debulking at the time of initial surgery was found to be a highly significant factor in patients with carcinosarcoma with regard to determining outcome (median survival of 14.8 months for patients with optimally debulked International Federation of Gynecology and Obstetrics Stage III disease vs. 3.1 months for patients with suboptimally/nondebunked Stage III disease; $P < 0.001$).

CONCLUSIONS. Ovarian carcinosarcoma is a distinct entity with a poor prognosis. Patients with carcinosarcoma differ from those with SAC with regard to having an older mean age of onset, an inferior response to platinum-based chemotherapy, and worse progression-free and cause-specific survival. The extent of benefit from chemotherapy is unclear. *Cancer* 2004;100:2148–53.

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KEYWORDS: carcinosarcoma, malignant mixed mesodermal tumor (MMMT), ovary, serous adenocarcinoma (SAC), chemotherapy, survival.

Carcinosarcomas (also termed malignant mixed mesodermal tumors [MMMTs], sarcomatoid carcinomas, or malignant mixed müllerian tumors) are relatively rare gynecologic tumors that occur throughout the female genital tract, most commonly in the uterus. Ovarian carcinosarcomas are reported to represent < 2% of ovarian malignancies.¹

Histologically, carcinosarcomas are epithelial tumors that are comprised of both a carcinomatous and sarcomatous component. They are subclassified as “heterologous” or “homologous” according

to the presence or absence of a stromal component containing mesenchymal tissue not normally found at the primary tumor site. Previously, it was believed that heterologous carcinosarcomas carried a worse prognosis, but recent evidence suggests that this histologic feature does not significantly alter prognosis.²

The pathogenesis of carcinosarcomas remains under debate but immunologic studies and molecular studies have suggested that both malignant elements (carcinoma and sarcoma) originate from a common epithelial stem cell (the combination theory) as opposed to two distinct malignant cell populations of different origin (the collision theory).^{1,3-14}

To our knowledge there are few studies published to date regarding ovarian carcinosarcomas involving large numbers of patients and the behavior and management of these tumors remains controversial. Generally, they present in a manner similar to carcinomas of the ovary with abdominal distension, pain, nausea, emesis, and weight loss. In some series, the pattern of spread was found to be similar to epithelial ovarian carcinoma, with early serosal and peritoneal dissemination.¹ Despite relatively high response rates to chemotherapy,¹⁵⁻¹⁷ patients with carcinosarcoma often quickly develop a recurrence and have a poor prognosis. Long-term survival is an unlikely prospect but is determined mainly by curative primary surgery in early-stage tumors. Although chemotherapy is commonly utilized in the setting of advanced disease, to our knowledge its role in the adjuvant setting has not been clarified in the context of randomized controlled trials.

In the current study, we report a review of prospectively recorded data concerning the clinical characteristics, management, and outcome of 65 patients with MMT compared with a group of 746 patients with serous adenocarcinoma (SAC). To the best of our knowledge, this is the largest carcinosarcoma cohort reported to date.

MATERIALS AND METHODS

Between 1984 and 2002, a total of 1568 patients with epithelial ovarian carcinoma and 70 patients with ovarian carcinosarcoma underwent treatment at the Edinburgh Cancer Centre, Western General Hospital, Edinburgh, U.K. (Table 1). Baseline variables were recorded prospectively, including age, World Health Organization (WHO) performance status, CA 125 level, tumor stage, and histologic subtype. In all cases, a histologic diagnosis of carcinosarcoma was confirmed by review of sections by a gynecologic pathologist. Of this group of 70 patients, 5 were excluded due to prior malignancy. A total of 746 patients with SAC were selected as a control group for a comparison of prog-

TABLE 1
Characteristics of Patients with MMT and Patients with SAC^a

| | MMT | SAC | |
|--------------------------------|------------|-------------|------------------|
| Total no. of patients | 65 | 746 | |
| Mean age (yrs) (SD) | 66.6 (9.2) | 62.0 (11.4) | <i>P</i> < 0.001 |
| FIGO Stage I | 6 (9%) | 68 (9%) | |
| Stage II | 6 (9%) | 57 (8%) | |
| Stage III | 41 (63%) | 471 (63%) | |
| Stage IV | 11 (17%) | 142 (19%) | |
| Unknown stage | 1 (2%) | 8 (1%) | |
| Optimally debulked (< 2 cm) | 28 (43%) | 305 (41%) | |
| Suboptimally debulked (> 2 cm) | 27 (42%) | 377 (51%) | |
| Unknown debulking status | 10 (15%) | 64 (9%) | |
| Homologous tumor | 18 (28%) | | |
| Heterologous tumor | 36 (55%) | | |
| Unknown | 11 (17%) | | |

MMT: malignant mixed mesodermal tumor; SAC: serous adenocarcinoma; SD: standard deviation; FIGO: International Federation of Obstetrics and Gynecology.

^a Differences were not significant except when noted.

TABLE 2
Chemotherapy Regimens used

| | MMT | SAC |
|------------------------------|----------|-----------|
| Platinum-containing regimens | 37 (57%) | 545 (73%) |
| Single-agent platinum | 32 (49%) | 329 (44%) |
| Platinum plus taxane | 0 (0%) | 87 (12%) |
| Platinum plus other drugs | 5 (8%) | 129 (17%) |
| Nonplatinum | 6 (9%) | 88 (12%) |
| No chemotherapy | 22 (34%) | 113 (15%) |
| Total | 65 | 746 |

MMT: malignant mixed mesodermal tumor; SAC: serous adenocarcinoma.

nosis (patients with a prior malignancy again were excluded).

Using the International Federation of Gynecology and Obstetrics (FIGO) classification, disease was staged by surgical findings at the time of diagnosis and by computed tomography (CT) scan. All surgery was performed according to agreed-upon U.K. standards by either a specialist in gynecologic oncology or a gynecologist with a special interest in gynecologic oncology.

Chemotherapy was administered to 43 of 65 patients with carcinosarcoma (Table 2). The platinum-containing regimens included carboplatin (21 patients), cisplatin (11 patients), a combination of cisplatin and doxorubicin (3 patients), a combination of cisplatin and ifosfamide (1 patient), and a combination of carboplatin and altretamine (1 patient). The nonplatinum-containing regimens included doxorubicin and ifosfamide (one patient), chlorambucil (three patients), etoposide (one patient), and treosul-

phan (one patient). The remaining patients did not receive chemotherapy because of a number of factors including poor performance status/comorbidity (12 patients), advanced age (4 patients), patient refusal (3 patients), and early-stage disease (1 patient). For two patients, the reason for not receiving chemotherapy was unknown.

For patients with measurable disease, response to chemotherapy was evaluated by CT according to WHO response criteria.¹⁸ A complete response (CR) was defined as the complete disappearance of all clinically detectable disease for at least 4 weeks. A partial response (PR) was defined as a > 50% decrease in the sum of the products of the largest perpendicular dimensions of all measurable or evaluable lesions for at least 4 weeks without an increase in the size of any known lesion or the appearance of a new lesion. No change was defined as a < 50% decrease and < 25% increase in the sum of measurable or evaluable lesions for at least 6 weeks. Progressive disease was defined as the appearance of a new lesion or a > 25% increase in the sum of measurable or evaluable lesions.

For patients without measurable disease on CT scan, response to chemotherapy was calculated according to CA 125 response using the criteria of Rustin et al.^{19,20}

Patient survival distribution was calculated using the Kaplan–Meier method. The survival analysis was performed based on disease-specific survival because 11 patients (10 patients with SAC and 1 with carcinosarcoma) died of causes other than ovarian carcinoma and were free of disease at the time of death. These findings are very similar to those obtained by all-cause mortality analysis. The significance of the survival distribution in each group was tested with the log-rank test.

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. The mean age of patients with carcinosarcoma (66.6 years) was significantly higher than that of patients with SAC (62.0 years) ($P < 0.001$). Of those patients for whom a baseline performance status was recorded (42% of those with carcinosarcoma and 61% of those with SAC), 30% of patients with carcinosarcoma had a WHO performance status of 3–4 compared with 8% of those with SAC ($P < 0.001$). Of the 65 patients with carcinosarcoma, 6 patients (9%) had Stage I disease [T1N0M0], 6 patients (9%) had Stage II disease [T2N0M0], 41 patients (63%) had Stage III disease [T3N0M0 or any T,N1], and 11 patients (17%) had Stage IV disease [any T any N, M1] according to the FIGO classification. The stage distribution was similar

TABLE 3
Response to Platinum-Based Chemotherapy

| | | No. of patients | Response | | | | Response rate (%) | |
|--------|--------|-----------------|----------|-----|-------------|----|-------------------|------------|
| | | | CR | PR | NC | PD | | |
| Rad | MMMT | 12 | 1 | 2 | 2 | 7 | 25 | $P = 0.02$ |
| | SAC | 258 | 54 | 101 | 42 | 61 | 60 | |
| | | | Response | | No response | | | |
| CA 125 | MMMT | 17 | 7 | | 10 | | 41 | $P = 0.08$ |
| | Serous | 331 | 207 | | 124 | | 63 | |

CR: complete response; PR: partial response; NC: no change; PD: progressive disease; Rad: radiologic response; MMT: malignant mixed mesodermal tumor; SAC: serous adenocarcinoma; CA 125: CA 125 response.

between patients with carcinosarcoma and those with SAC. A lower proportion of patients with carcinosarcoma were found to have ascites at the time of presentation (67%) compared with patients with SAC (78%) ($P = 0.05$). Approximately 74% of patients with carcinosarcoma had an elevated baseline CA 125 level after surgery compared with 85% of patients with SAC ($P = 0.095$). Using the reverse Kaplan–Meier method, the overall median duration of follow-up was 84 months (42 months for patients with MMT and 86 months for patients with SAC [range, 1–228 months]).

Clinical Outcome

Fourteen patients with Stage III/IV carcinosarcoma (27%) had radiologically measurable disease after initial surgery, 12 of whom received platinum-based chemotherapy. One of these patients achieved a CR (8%) and 2 patients achieved a PR (17%) (Table 3); thus, the overall objective response rate was 25%. Progressive disease was documented in 7 patients (58%) and no change was documented in 2 patients. Using CA 125 as a method of assessing response, 7 of 17 patients (41%) achieved a response to platinum-based chemotherapy according to criteria of Rustin et al.^{19,20} There were 10 patients who had evaluable disease based on Rustin et al.'s CA 125 criteria who did not have radiologically measurable disease. Two patients with evaluable disease were treated with nonplatinum-based chemotherapy; neither achieved a response.

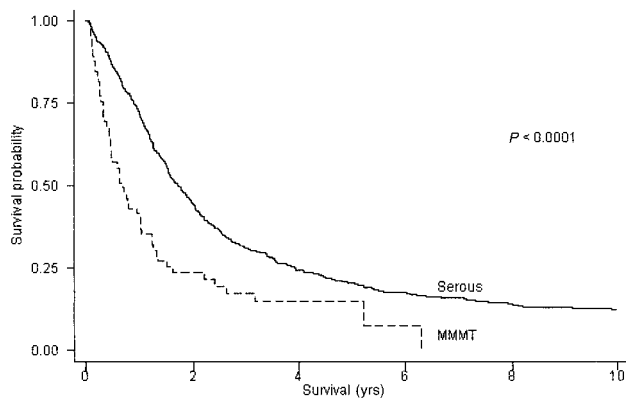
Three hundred two patients with Stage III/IV SAC (49%) were found to have measurable disease after surgery. Of the 258 patients who received platinum-based chemotherapy, 54 patients (21%) achieved a CR and 101 (39%) achieved a PR to platinum-based chemotherapy; thus, the overall objective response rate was 60%. Progressive disease was documented in 61

TABLE 4
Estimated Survival Rate for MMT versus SAC by Stage of Disease

| FIGO Stage | MMMT | | | SAC | | |
|------------|-----------------|---------------|---------------|-----------------|---------------|---------------|
| | No. of patients | 2-yr survival | 5-yr survival | No. of patients | 2-yr survival | 5-yr survival |
| I | 6 | 83% | 83% | 68 | 94% | 76% |
| II | 6 | 0 | 0 | 57 | 75% | 32% |
| III | 41 | 22% | 0 | 471 | 39% | 15% |
| IV | 11 | 0 | 0 | 142 | 23% | 3% |
| All stages | 65 | 23% | 15% | 746 | 44% | 20% |

 $P < 0.0001$

MMMT: malignant mixed mesodermal tumor; SAC: serous adenocarcinoma; FIGO: International Federation of Gynecology and Obstetrics.

**FIGURE 1.** Kaplan-Meier estimated survival for patients with serous adenocarcinoma (bold line) and malignant mixed mesodermal tumor (MMMT) (dotted line).

patients (24%) and no change was documented in 42 patients (16%). The CA 125 response rate was 63%.

Recurrence of carcinosarcoma occurred in 50% of Stage I patients (3 of 6 patients), 100% of Stage II patients (6 of 6 patients), 90% of Stage III patients (37 of 41 patients), and 100% of Stage IV patients (11 of 11 patients). The median time to disease recurrence was 6.4 months. The median time to recurrence in patients with SAC was 12.1 months.

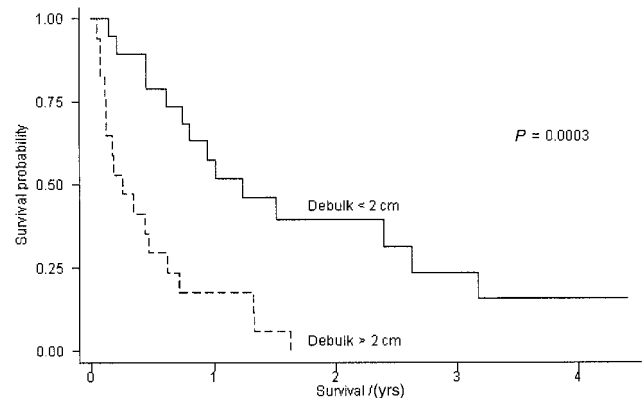
In those patients with carcinosarcoma, the median survival time was 75.5 months in patients with Stage I disease, 5.1 months in patients with Stage II disease, 8.5 months in patients with Stage III disease, and 5.5 months in patients with Stage IV disease. In the patients with SAC, the median survival time was 164.2 months in patients with Stage I disease, 45.7 months in patients with Stage II disease, 18.5 months in patients with Stage III disease, and 15.0 months in patients with Stage IV disease.

Overall, patients with ovarian carcinosarcoma had

TABLE 5
Estimated Survival Rate of Patients with FIGO Stage III Disease Based on Size of Residual Tumor

| Initial surgery | MMMT | | SAC | |
|-----------------------|---------------|---------------|---------------|---------------|
| | 2-yr survival | 5-yr survival | 2-yr survival | 5-yr survival |
| < 2 cm residual tumor | 39% | 0 | 61% | 33% |
| > 2 cm residual tumor | 0 | 0 | 26% | 4% |

FIGO: International Federation of Gynecology and Obstetrics; MMTT: malignant mixed mesodermal tumor; SAC: serous adeno- carcinoma.

**FIGURE 2.** Kaplan-Meier estimated survival for patients with International Federation of Gynecology and Obstetrics Stage III malignant mixed mesodermal tumor with optimally debulked (< 2 cm) (bold line) and suboptimally debulked/nondebulked (> 2 cm) (dotted line) disease.

a median survival of 8.2 months, a 2-year survival rate of 23% and a 5-year survival rate of 15% (Table 4) (Fig. 1). In the patients with SAC, the overall median survival was 20.7 months with a 2-year survival rate of 44% and a 5-year survival rate of 20%. The difference in overall survival between the groups was found to be highly statistically significant ($P < 0.0001$).

Table 5 and Figure 2 show the estimated survival rates in patients with Stage III carcinosarcoma when such patients are divided into 2 groups: a group with < 2 cm residual disease after initial surgery ("optimally debulked") and a group with > 2 cm residual tumor ("suboptimally/nondebulked"). The 19 patients with Stage III carcinosarcoma who were in the "optimally debulked" group had a median survival of 14.8 months with a 2-year survival rate of 39%. The 17 patients in the "nondebunked/ suboptimally debulked" group had a significantly lower median survival of 3.1 months ($P < 0.001$) and a 2-year survival rate of 0%.

DISCUSSION

It has been suggested from previous studies that ovarian carcinosarcoma is a relatively rare clinicopathologic entity that has a tendency to affect an elderly population and is associated with poor prognosis. In the current series, we found that carcinosarcomas represented 4% of the total number of epithelial ovarian carcinomas, which to our knowledge is a higher proportion than previously described.¹ It was confirmed that carcinosarcoma tends to affect a more elderly population than does SAC, with the mean age of patients with carcinosarcoma (66.6 years) being significantly older than that of patients with SAC (62.0 years). Patients with carcinosarcoma were more likely to have a poor performance status, with 30% of patients having a WHO performance status of 3–4 at baseline compared with only 8% of patients with SAC. Although this difference is statistically significant, it should be interpreted with caution because only 42% of patients with carcinosarcoma had a baseline performance status recorded (compared with 61% of patients with SAC). There was a similar stage distribution in the carcinosarcoma and SAC groups, with the majority of patients having advanced disease (Stage III/IV) at the time of presentation (80% of patients with carcinosarcoma vs. 82% with SAC). There appeared to be a higher proportion of patients with carcinosarcoma who had a negative CA 125 level (i.e., within the reference range) at baseline (26%) compared with patients with SAC (15%), although this difference was not found to be statistically significant.

To our knowledge, there is no well established consensus regarding which patients with carcinosarcoma should receive chemotherapy and which chemotherapy regimen(s) should be regarded as optimum. This uncertainty may in part be reflected in the variety of different chemotherapy regimens used in the current series and the relatively higher proportion of patients with carcinosarcoma compared with SAC who did not receive chemotherapy as part of their management (34% vs. 15%). The response rate to platinum-based chemotherapy for patients with carcinosarcoma was found to be 25%, a rate that is inferior to the previously published data of between 33–47%.^{15–17} A significantly inferior response rate of carcinosarcoma to platinum-based chemotherapy compared with SAC was confirmed (25% vs. 60%; $P = 0.02$). The published data concerning response to chemotherapy in ovarian carcinosarcoma is comprised of a number of relatively small series collected over many years using a number of different chemotherapy regimens, the majority of which were platinum-based. In what to our knowledge is the largest series published to date,

which was reported by Harris et al.¹⁵ and was comprised of 40 patients, the majority of patients received platinum-based chemotherapy. The response rate was 40% with an overall median survival of 8.7 months. Prendeville et al.¹⁶ reported a series of 20 patients, 15 of whom received chemotherapy. The regimens used were predominantly based on cyclophosphamide, with the minority of patients receiving platinum. The response rate was 47% with a median survival of 14 months. Chang et al.¹⁷ reported a series of 37 patients, the majority of whom received platinum-based chemotherapy, either as a single agent or in a variety of combinations. The response rate was 33% with a median survival of 8 months.

In the current study, only 18 of 65 patients with carcinosarcoma had CA 125 measurements that allowed a response to be assessed according to the criteria established by Rustin et al.^{19,20} Of these 18 patients, 5 were found to have a CA 125 response who did not have radiologically evaluable disease; 1 patient achieved a CA 125 response despite being found to have stable disease on CT scan. The remainder of the CA 125 results demonstrated a trend that largely mirrored those observed on radiologic assessment. To our knowledge, assessing response according to CA 125 using the criteria of Rustin et al.^{19,20} has not been validated for use in carcinosarcoma but does appear to provide a useful marker of response in some patients who do not have radiologically measurable disease and therefore may provide useful information in these patients to augment that gained from clinical assessment.

The overall median survival for patients with carcinosarcoma was found to be poor (8.2 months) and was significantly shorter than the median survival for patients with SAC (20.7 months). Survival did not appear to be influenced by the presence of heterologous elements observed on pathology. A statistically significant survival benefit for those patients with Stage III carcinosarcoma in whom optimal debulking was achieved at surgery was confirmed. This emphasizes the importance of an aggressive surgical approach in patients with Stage III carcinosarcoma.

The results of the current study confirm that carcinosarcomas differ from SACs with regard to their age at onset and response to platinum-based chemotherapy. A more aggressive clinical course and a worse survival than SACs is confirmed. Optimal debulking at the time of surgery appears to be of prognostic significance but to our knowledge the optimal use of chemotherapy has yet to be identified fully.

These results emphasize the need to recognize ovarian carcinosarcoma as a distinct clinicopathologic entity that requires a different strategy in its manage-

ment compared with SAC that takes into account the older population, their often poor performance status, and their relative resistance to platinum-based chemotherapy. To our knowledge, no randomized evidence exists for a survival benefit from chemotherapy of any kind for ovarian carcinosarcoma. Therefore, there is a clear need for randomized controlled trials to explore the optimum role of chemotherapy in ovarian carcinosarcoma.

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